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| 10/525,341   | 07/06/2005  | Miroslav Veverka     | 262999US0PCT        | 3636             |
| 22850  | 7590        | 05/21/2009           |                     |                  |
| OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, P.C.<br>1940 DUKE STREET<br>ALEXANDRIA, VA 22314 |             |                      |                     |                  |
| EXAMINER   |             |                      |                     |                  |
| CHANG, CELIA C   |             |                      |                     |                  |
| ART UNIT   |             | PAPER NUMBER         |                     |                  |
| 1625   |             |                      |                     |                  |
| NOTIFICATION DATE  |             | DELIVERY MODE        |                     |                  |
| 05/21/2009   |             | ELECTRONIC           |                     |                  |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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### Office Action Summary

**Application No.**

10/525,341

**Applicant(s)**

VEVERKA ET AL.

**Examiner**

Celia Chang

**Art Unit**

1625

**Period for Reply** -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on 03 March 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1, 3, 5, 6, 8 and 10 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 3, 5, 6, 8 and 10 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-8508)
- Paper No(s)/Mail Date \_\_\_\_\_

- 4) ☐ Interview Summary (PTO-413)
- Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### DETAILED ACTION

1. This application is a RCE of SN 10/525,342.

Claims 2, 4, 7, 9, 11-12 have been canceled. Claims 1, 3, 5-6, 8, 10 are pending.

2. Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. \*\*\*.

The limitation "1.1-1.5 equivalent of sulfuric acid" lacks antecedent basis in the specification. Please note that no description of a "range" was found in the specification. A range was found in *original* claim 3 which is 0.6-1.1 equivalent.

The "1.1-1.5" equivalent range is therefore new matter. Removal of all new matter is required. In re Russussen 210 USPQ 325.

3. Claims 1, 3, 5-6, 8 and 10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Process of making polymorphic forms of a defined compound is very specific and unpredictable. The state of the art of polymorph recovery is highly unpredictable. See for example *Kirk-Othmer Encyclopedia of Chemical Technology* Copyright © 2002 by John Wiley & Sons, Inc., pp. 95-147, Article Online Posting Date: August 16, 2002 (provided in previous office action). This article indicates that many uncertain factors determine morphology, and specifically that the appearance of the crystalline product and its processing characteristics (such as washing and filtration) are affected by crystal habit (i.e., the general shape of a crystal). Relative growth rates of the faces of a crystal determine its shape. Faster growing faces become smaller than slower growing faces and, in the extreme case, may disappear from the crystal altogether. Growth rates depend on the presence of impurities, rates of cooling, temperature, solvent, mixing, and supersaturation. Furthermore, the importance of each of these factors may vary from one crystal face to another, see page 114.

Art Unit: 1625

The reference also teaches that polymorphism is a condition wherein crystalline form is intimately associated with processing ("Polymorphism is a condition in which chemically identical substances may crystallize into different forms. Each form is, however, only stable (thermodynamically) in a certain range of temperature and pressure. In the case of ambient pressure, eg, ammonium nitrate exhibits four changes in form between -18 and 125°C:

liquid  $\xleftrightarrow{160.6^{\circ}\text{C}}$  cubic  $\xleftrightarrow{125.2^{\circ}\text{C}}$  trigonal  $\xleftrightarrow{84.3^{\circ}\text{C}}$  orthorhombic I  $\xleftrightarrow{32.3^{\circ}\text{C}}$  orthorhombic II  $\xleftrightarrow{-18^{\circ}\text{C}}$  tetra

Transitions from one polymorphic form to another may be accompanied by changes in process conditions (temperature, pressure, shear or solution composition), transitions from one polymorphic form to another and lead to formation of a solid product with unacceptable properties (eg, melting point or dissolution rate).

The Mukarram et al. WO 2005/012300 reference (provided in previous office action) provided evidence that the instant claimed process is inoperable in producing form I exclusively (see '300 p.3 paragraphs after structural formula). Specifically, Mukarram '300 disclosed that form I without contamination of other forms would have a higher melting point between 198-200°C. All the examples made from the instantly claimed process being evidence in the specification have melting points of 184-186°C, thus, are inoperable for making exclusively form I.

In the prior art, it was also evidenced that when crystallization was conducted under the conditions and parameters of Lifshitz et al. US 6,767,913, using 2-propanol, the clopidogrel hydrogen sulfate form IV was formed (see col. 21, lines 58-60) after reflux and cooled to room temperature. When crystallization was conducted under the conditions and parameters of Lifshitz et al. '913, using 2-butanol, the clopidogrel hydrogen sulfate form V is formed (see col. 22, lines 35-40) after reflux and cooled to room temperature.

The instant specification provided process for making form I with exactly the steps and conditions of the instant examples 1-6, i.e. dissolving clopidogrel free base in 2-propanol or n-butylacetat, adding 0.6-1.1 equivalent concentrated sulfuric acid at 0 to -5°C or 0 to +5°C, stirring the mixture at -5°C and 15°C. The final filtration temperature can be higher (i.e. 20-24°C) when n-butylacetate was used but the process of 2-propanol are operable exclusively under "cooling" temperature (none room temperature). In addition, the cooling temperature and

Art Unit: 1625

the slow elevation of temperature to between 10-15°C is the critical step for obtaining the product with the disclosed physical properties.

In view of the high degree of unpredictability and the evidence in the prior art that temperature is an essential element in controlling purity of "forms", the "claimed scope" lacks descriptive and enablement supported from the specification.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3, 5-6, 8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bardore et al. US 4,847,265 or Bousquet et al. US 6,429,210 in view of Lifshitz-Liron et al. US 7,074,928 supplemented with Mukarram et al. WO 2005/012300 (US 7,291,735) (all previously provided)

*Determination of the scope and content of the prior art (MPEP §2141.01)*

Bardore et al. '265 or Bousquet et al. '210 disclosed process of making the same claimed product which has a m.p. of 184°C, see '265 col. 6, example 1(e) lines 47-64, or '210 col. 9, lines 44-60, example 1B.

*Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)*

The difference between the instant claims and the prior art process is that instead of acetone, the instant claims employed alcohol, esters or mixture thereof. Lifshitz-Liron et al. US 7,074,928 taught that variation of solvent such as ether may be employed to obtain the same product (col. 19-20 examples of form I). Mukarram et al. '300 taught that the same product obtained with acetone can be obtained using solvents such as alcohol or ether (see p.2, paragraph after structural formula).

Art Unit: 1625

*Finding of prima facie obviousness—rational and motivation (MPEP§2142-2143)*

One having ordinary skill in the art would be motivated to employ variation of solvents in obtaining the same product because one has been suggested that similar organic solvent would give the same product as evidenced by the per ponderous of references i.e. '265, '210, '928 and '300, that changing solvents is a routine choice by the person having ordinary skill and lower alkanoyl-lower alcohol esters are common laboratory solvents.

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang, Ph. D. whose telephone number is 571-272-0679. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres, Ph. D., can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

OACS/Chang  
May 18, 2009

/Celia Chang/  
Primary Examiner  
Art Unit 1625